RESEARCH PAPER

A Prospective Clinical Study on the Neuroprotective Evaluation of Angiotensin Type 1 (AT1) Receptor Blockers Combined with an Excitatory Amino Acid Transporter-2 (EAAT-2) Activator in Patients with Cerebral Ischemia: A Review Article

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ABSTRACT

Cerebral ischemia remains a major cause of mortality and long-term disability despite advances in reperfusion therapy, because a substantial proportion of patients continue to experience progressive neuronal injury driven by excitotoxicity, oxidative stress, microvascular dysfunction, blood–brain barrier disruption, and neuroinflammation [1][2][3]. Angiotensin II type 1 receptor signaling contributes to ischemic injury through vasoconstriction, inflammatory amplification, matrix metalloproteinase activation, edema formation, and endothelial dysfunction, whereas pharmacologic AT1 receptor blockade has shown neuroprotective effects in experimental stroke models that include reduced infarct volume, reduced edema, improved neurologic scores, and partial preservation of cerebral blood flow [4][5][6][7]. In parallel, the astrocytic glutamate transporter EAAT-2 is a central determinant of extracellular glutamate clearance, and reduced transporter activity during ischemia is associated with excitotoxic neuronal death; strategies that increase EAAT-2 expression or function, including ceftriaxone and experimental EAAT-2-enhancing approaches, have demonstrated neuroprotective potential in preclinical models [8][9][2][10].

The therapeutic concept of combining an AT1 receptor blocker with an EAAT-2 activator is biologically attractive because it targets two complementary arms of ischemic injury: angiotensin-driven neurovascular inflammation and glutamate-mediated excitotoxicity [11][12][3]. Available evidence suggests that AT1 receptor blockade may reduce inflammatory conditions that impair glutamate transporters, while EAAT-2 activation may directly limit glutamate accumulation in the ischemic penumbra, thereby extending the viability of salvageable tissue [11][5][2]. However, direct clinical evidence for the combination in patients with cerebral ischemia is lacking, and no established randomized clinical pathway currently supports routine use specifically for this purpose [13].

This review synthesizes mechanistic, preclinical, and translational evidence relevant to a prospective clinical evaluation of AT1 receptor blockers combined with an EAAT-2 activator in cerebral ischemia. It proposes a clinically relevant review framework covering pathophysiology, pharmacologic rationale, candidate agents, safety considerations, endpoints, and manuscript-ready discussion points for publication. The cumulative evidence supports the combination as a promising hypothesis-generating neuroprotective strategy that merits carefully designed prospective clinical testing rather than immediate therapeutic adoption [11][12][13].

Keywords: Cerebral ischemia, AT1 receptor blocker, EAAT-2 activator, neuroprotection, excitotoxicity, angiotensin, glutamate transporter

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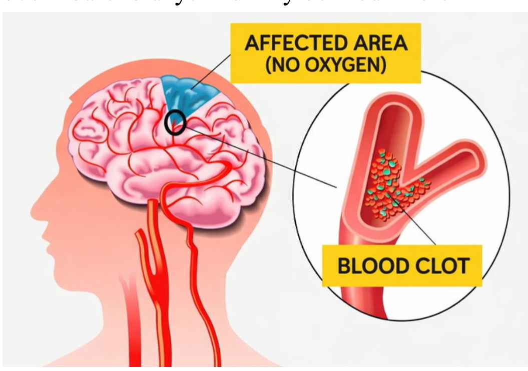
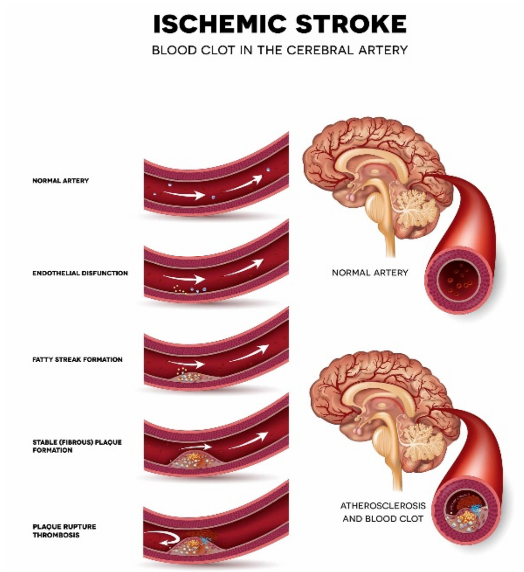
Introduction

Ischemic stroke develops when cerebral blood flow falls below the threshold required to sustain neuronal metabolism, initiating a cascade of energy failure, membrane depolarization, glutamate accumulation, intracellular calcium overload, mitochondrial dysfunction, oxidative stress, and inflammatory injury [1][2][3]. Although reperfusion therapies can restore perfusion in selected patients, many patients either present outside the treatment window or suffer substantial secondary injury despite recanalization, creating an urgent need for adjunctive neuroprotective therapies [13][3]. The ischemic penumbra, a zone of impaired but potentially recoverable tissue surrounding the infarct core, remains the principal therapeutic target for such interventions because Patho biologic processes in this region evolve over hours to days and may be modifiable [1][2].



Among the multiple molecular pathways implicated in cerebral ischemia, two are especially relevant to the proposed combination strategy. The first is overactivation of the brain and cerebrovascular angiotensin II/AT1 receptor axis, which promotes vasomotor dysregulation, oxidative injury, cytokine signaling, and edema formation [14][5][7]. The second is failure of astrocyte-mediated glutamate clearance, especially through EAAT-2, the predominant glutamate transporter responsible for most extracellular glutamate uptake in the central nervous system [15][2][10]. When these pathways operate together, excessive glutamate exposure and inflammatory neurovascular injury reinforce one another, worsening neuronal death and limiting functional recovery [11][1][3].



Angiotensin receptor blockers are widely used cardiovascular drugs with established safety profiles in hypertension and related disorders, making them attractive candidates for repurposing in stroke neuroprotection [4][7]. Likewise, ceftriaxone and other EAAT-2-enhancing approaches have been explored for their ability to improve glutamate transport and reduce excitotoxic damage, although their clinical translation remains incomplete [9][16][10]. A review article centered on the combined neuroprotective evaluation of AT1 receptor blockers and an EAAT-2 activator is therefore timely, because it integrates converging neurovascular and astroglial mechanisms into a clinically testable framework [11][12].

Clinical Question and Review Objective

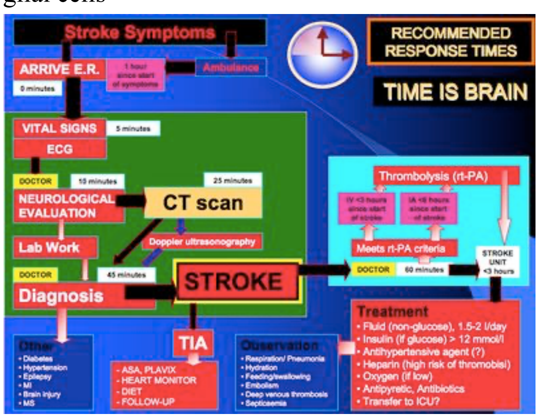
The central review question is whether combining an AT1 receptor blocker with an EAAT-2 activator could provide additive or synergistic neuroprotection in patients with cerebral ischemia by simultaneously reducing angiotensin-mediated inflammatory injury and glutamate-mediated excitotoxicity [11][12][3]. This question is clinically relevant because monotherapy neuroprotection in stroke has historically produced inconsistent results, often due to the multifactorial nature of ischemic injury [13][3]. Combination strategies are more likely to succeed when they address parallel mechanisms within the ischemic cascade [1][2].

The objective of this review is to assemble a manuscript-ready synthesis of mechanistic evidence, animal data, translational considerations, and proposed clinical design elements for future prospective studies [17][13].

Pathophysiology of Cerebral Ischemia

Ischemic Cascade

Interruption of cerebral perfusion rapidly depletes glucose and oxygen delivery, suppresses ATP production, and impairs ion pump activity, which leads to membrane depolarization and uncontrolled neurotransmitter release [1][3]. Excess extracellular glutamate then overstimulates ionotropic glutamate receptors, especially NMDA receptors, causing calcium influx, protease activation, free radical generation, and activation of cell death pathways [1][2][3]. These events are amplified by mitochondrial failure, acidosis, and disruption of ionic homeostasis in neurons and glial cells [2][3].



Neuroinflammation and Edema

As ischemia progresses, endothelial activation, microglial stimulation, cytokine release, and matrix metalloproteinase induction contribute to blood–brain barrier breakdown and vasogenic edema [4][5]. This inflammatory environment increases tissue swelling, worsens perfusion in the penumbra, and facilitates delayed neuronal loss [4][5][1]. The angiotensin II/AT1 pathway is strongly implicated in these later injury phases because it modulates both vascular tone and inflammatory signaling [14][5].

Glutamate Transport Failure

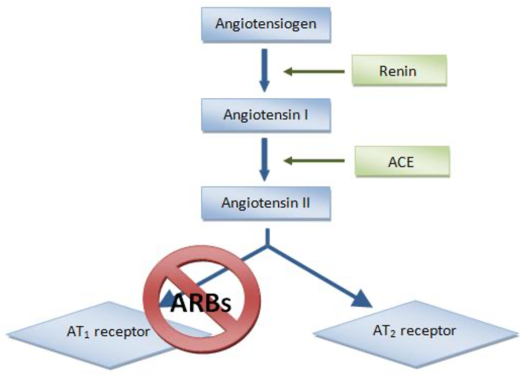
EAAT-2, predominantly expressed in astrocytes, normally clears the majority of synaptic glutamate and thereby limits excitotoxicity [15][2][10]. During ischemia, transporter dysfunction or downregulation reduces glutamate uptake capacity, so extracellular glutamate rises and becomes directly neurotoxic [11][2][3]. This mechanism is especially important in the penumbra, where partial tissue viability means that preserving glutamate homeostasis may translate into meaningful functional protection [1][2].

Role of the Renin–Angiotensin System in Ischemic Brain Injury

The brain renin–angiotensin system is increasingly recognized as an active participant in ischemic injury rather than a purely systemic blood pressure regulator [14][18]. AT1 receptor activation in cerebrovascular and neural tissues can increase vasoconstriction, oxidative stress, inflammatory transcription, and protease activity, all of which contribute to infarct expansion and neurologic deterioration [4][14][5]. Experimental studies also suggest that Ang II signaling worsens cerebral edema and mortality after ischemia, providing a rationale for therapeutic blockade [4].

AT1 receptor blockade appears beneficial through multiple mechanisms. It can improve cerebral hemodynamics, reduce matrix metalloproteinase expression, attenuate inflammatory mediators, decrease edema, and reduce tissue injury even at doses that do not produce major systemic hypotension in some animal models. This finding is clinically important because excessive blood pressure reduction in acute ischemic stroke may compromise collateral perfusion, whereas a neuroprotective dose independent of marked hemodynamic lowering would be more attractive for translational use [4][5].

AT1 Receptor Blockers as Neuroprotective Agents



Candesartan

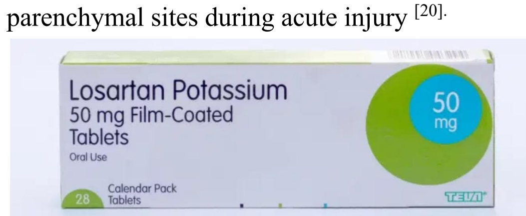
Candesartan is among the most consistently studied ARBs in experimental cerebral ischemia. Preclinical work shows that candesartan can reduce infarct size, improve neurologic outcomes, attenuate edema, and in some settings increase cerebral blood flow, including when administered around reperfusion rather than only as chronic pretreatment [5][6][7]. Additional evidence from chronic cerebral hypoperfusion models suggests antioxidant-related effects, including attenuation of biochemical markers of oxidative damage [19].

Olmesartan

Olmesartan has also shown neuroprotective effects in transient focal cerebral ischemia models. In one rat study, Olmesartan improved stroke index score, infarct volume, and cerebral edema, and some benefits were observed even at a low dose that did not lower blood pressure, suggesting a direct tissue-protective effect beyond antihypertensive action [4]. The same report linked these effects with reduced upregulation of matrix metalloproteinases in ischemic tissue, reinforcing the anti-inflammatory and anti-edema rationale [4].

Losartan and Irbesartan

Available experimental literature also supports potential benefit with losartan and irbesartan, although the depth of evidence is less uniform than for candesartan [20]. A comparative experimental report found that systemically administered candesartan, irbesartan, and losartan can produce central AT1 receptor inhibition after ischemia depending on blood–brain barrier penetration and dosing, highlighting pharmacokinetic factors that may influence translational success [20]. This issue is critical because clinical efficacy may depend not only on receptor affinity but also on the capacity of an ARB to reach relevant cerebrovascular and parenchymal sites during acute injury [20].



EAAT-2 Biology and Therapeutic Relevance

EAAT-2, also referred to as GLT-1 in rodent literature, is the dominant astrocytic glutamate transporter responsible for most extracellular glutamate clearance in the mammalian brain

[15][10]. Because glutamate excitotoxicity is a central mechanism of neuronal damage after ischemia, enhancing EAAT-2 expression or function is a biologically compelling therapeutic strategy [1][2][3]. Experimental overexpression of EAAT2 in astrocytes has been shown to increase neuroprotection after moderate hypoxia/ischemia, demonstrating that the transporter itself is a valid mechanistic target rather than a mere biomarker [8].

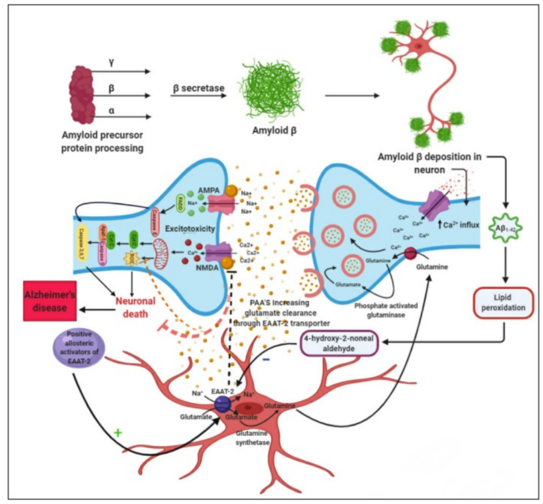
Studies of ischemia-triggered excitotoxicity emphasize that transporter impairment contributes directly to extracellular glutamate accumulation, although reported changes in transporter expression after injury are not always fully consistent across models and time points [2]. Even with this variability, the broader translational implication remains stable: interventions that preserve or enhance glutamate transport may reduce excitotoxic burden and improve tissue survival [2][3].

EAAT-2 Activators and Candidate Drugs

Ceftriaxone

Ceftriaxone is the best-known pharmacologic EAAT-2 activator in translational neuroprotection research. Mechanistic studies show that ceftriaxone can induce EAAT2 expression and functional activity and exert neuroprotective effects against glutamate toxicity in ischemia-related experimental systems [10]. Additional preclinical work indicates that ceftriaxone can preserve EAAT1 and EAAT2 expression and reduce excitotoxic cell death under hypoxic or ischemia-relevant conditions [16].

However, ceftriaxone should not be presented as a fully validated stroke neuroprotectant. Some animal work has found increases in EAAT2 mRNA without corresponding strong protein overexpression or robust functional benefit, indicating that the magnitude of the effect may depend on model, timing, dose, age, and brain region. This mixed but still promising evidence supports ceftriaxone as a rational clinical candidate for hypothesis-driven study rather than as an established standard of care [10].



Other EAAT-2-Enhancing Strategies

Beyond ceftriaxone, several experimental strategies aim to enhance EAAT-2-mediated glutamate clearance, including gene transfer, cell-based therapies, and indirect regulatory targets [8][9]. Selective astrocytic overexpression of EAAT2 improved neuroprotection after moderate hypoxia/ischemia, while cell-based EAAT2-expressing systems have been proposed as novel glutamate-grabbing therapies in cerebral ischemia [8][9]. Moreover, inhibition of HSP90β in a rat MCAO model increased EAAT2 expression and improved neurologic deficits, supporting the general concept that EAAT-2 upregulation can be neuroprotective even when achieved through non-antibiotic pathways.

Why Combine AT1 Blockade with EAAT-2 Activation?

The proposed combination is mechanistically appealing because ischemic brain injury is not driven by a single pathway. AT1 receptor blockers target cerebrovascular dysregulation, inflammatory signaling, edema formation, and matrix metalloproteinase-related tissue injury, whereas EAAT-2 activators address glutamate accumulation and excitotoxic neuronal loss [4][5][10][3]. A combined regimen therefore has the potential to protect both the neurovascular unit and the astrocyte-neuron glutamate buffering system [11][2].

A particularly important conceptual link is that inflammation and oxidative stress can impair glutamate transporter function during cerebral ischemia, while ARBs may reduce inflammatory conditions that contribute to EAAT dysfunction [11][2]. In the same direction, a recent review explicitly framed the combination of ARBs and ceftriaxone as a novel approach for cerebral ischemia based on suppression of Ang II/AT1-driven neuroinflammation and enhancement of EAAT-2-mediated glutamate clearance [11][12]. Although this does not substitute for clinical trial evidence, it strengthens the biological plausibility and translational coherence of the combined strategy [11][12].

Translational Evidence Supporting Combination Therapy

Direct clinical evidence for ARB plus EAAT-2 activator therapy in ischemic stroke remains absent in the currently retrieved literature, but several converging lines of evidence support its evaluation. First, multiple preclinical studies report benefits with ARB monotherapy across infarct size, edema, neurologic score, and cerebral blood flow outcomes [4][5][6][7]. Second, several mechanistic and experimental studies indicate that increased EAAT-2 expression or activity can reduce glutamate-mediated injury and improve outcomes in ischemia-relevant models [8][9][16][10]. Third, a recent narrative review has already articulated the combination concept in the context of cerebral ischemia, which suggests that the idea has sufficient scholarly basis to justify a focused review article and future clinical investigation [11][12].

The translational challenge is that preclinical neuroprotection does not automatically predict human benefit. Human stroke is biologically heterogeneous with respect to time of presentation, vessel territory, reperfusion status, blood pressure profile, collateral circulation, and comorbid disease, all of which may influence treatment response [13][3]. As a result, any prospective clinical study evaluating this combination would need careful eligibility criteria and clinically meaningful endpoints rather than sole reliance on surrogate markers [13].

Candidate Clinical Agents for a Prospective Study

For the AT1 receptor blocker component, candesartan is an attractive candidate because it has one of the strongest and most repeated experimental datasets in cerebral ischemia, including evidence for reduced infarct size, edema attenuation, and improved neurologic outcome [5][6][7]. Olmesartan may also be considered because of data suggesting neuroprotection at doses not necessarily linked to substantial blood pressure lowering, which is useful in acute stroke settings where hypotension must be avoided [4]. Losartan and irbesartan remain alternatives, but the translational manuscript would be stronger if it prioritizes agents with more direct ischemia-focused evidence [20].

For the EAAT-2 activator component, ceftriaxone is the most defensible choice for a prospective clinical concept because it is widely available, clinically approved for other indications, and mechanistically linked to EAAT2 induction in multiple experimental studies [16][10]. Nevertheless, the manuscript should explicitly acknowledge the limitations of using ceftriaxone outside its anti-infective indication, especially the need to balance neuroprotective rationale against antimicrobial stewardship and uncertain magnitude of EAAT-2 activation in humans [17][13].

Proposed Review-Based Clinical Study Framework

Although this manuscript is a review article rather than an original trial report, presenting a model prospective study design can substantially improve its translational value. A plausible design would be a prospective, randomized, controlled, parallel-group clinical study in adult patients with acute cerebral ischemia confirmed by neuroimaging [13]. Patients could receive standard stroke care alone, standard care plus an ARB, standard care plus ceftriaxone, or standard care plus the ARB–ceftriaxone combination, depending on ethical feasibility and institutional approval [13].

Suggested Eligibility Criteria

Inclusion criteria may include adults with acute ischemic stroke within a defined therapeutic window, measurable neurologic deficit, and hemodynamic stability adequate for ARB exposure [13]. Exclusion criteria should include intracerebral hemorrhage, septic states already requiring antibiotic escalation, severe renal dysfunction, marked hypotension, hypersensitivity to the selected agents, and concurrent conditions that would confound neurologic outcome assessment [13]. Because ceftriaxone is an antibiotic, exclusion and stewardship criteria should be especially explicit.

Suggested Endpoints

Primary endpoints could include functional neurologic outcome scales at follow-up, such as improvement in standardized stroke disability measures, together with early safety outcomes [13]. Secondary endpoints may include infarct growth on imaging, mortality, edema-related complications, biomarker changes related to inflammation or glutamate handling, and length of hospital stay [4][5][3]. If feasible, mechanistic sub studies could evaluate biomarkers linked to MMP activity, inflammatory cytokines, or glutamate homeostasis to test whether the hypothesized dual mechanism is biologically engaged in humans [4][11].

Timing and Dosing Considerations

The timing of neuroprotection is likely critical. Experimental evidence suggests that ARB benefit may be seen with pretreatment, peri-ischemic use, or early reperfusion-associated administration, but translational studies must define a realistic human dosing window compatible with emergency stroke care [6][7]. Similarly, ceftriaxone-mediated EAAT-2 induction may not be instantaneous, so protocol design should consider whether the intervention is intended mainly to protect the penumbra acutely, to reduce delayed excitotoxic progression, or both [10].

Safety and Practical Considerations

The main safety concern for ARBs in acute cerebral ischemia is excessive blood pressure reduction, which could impair collateral flow in vulnerable tissue [4][5]. Therefore, any clinical protocol must define blood pressure thresholds, monitoring frequency, rescue procedures, and discontinuation criteria. The choice of dose should favor neurovascular protection without aggressive hypotensive effect whenever possible [4].

For ceftriaxone, major practical concerns include antimicrobial stewardship, allergy risk, biliary complications, superinfection, and the ethical question of prolonged antibiotic exposure for a non-infectious indication [16]. These concerns do not invalidate the concept, but they require strong justification, short and protocolized exposure periods, and possibly exploration of future non-antibiotic EAAT-2 activators [15]. A high-quality review should acknowledge that the ideal translational future may involve selective EAAT-2 modulators rather than long-term repurposing of broad-spectrum antibiotics [15].

Strengths of the Combination Hypothesis

Several features make the proposed combination attractive for academic and clinical discussion. The agents target complementary mechanisms, both components are supported by preclinical evidence, ARBs already have extensive clinical safety experience in cardiovascular medicine, and the biological rationale aligns with contemporary understanding of the neurovascular unit and astrocyte-mediated glutamate buffering [4][5][2][10]. In addition, the concept is novel enough to support a focused review article while remaining sufficiently grounded in established stroke pathophysiology to avoid appearing speculative [11][12].

Another strength is the potential applicability to patients who are not candidates for reperfusion therapy or who need adjunctive post-reperfusion protection. Because secondary injury continues after vessel reopening, therapies that reduce inflammation and excitotoxicity could complement rather than compete with thrombolysis or thrombectomy pathways [13][3]. This translational positioning is useful when preparing the discussion section for publication [13].

Limitations and Evidence Gaps

The most important limitation is the lack of direct human clinical trial evidence for the combined use of an AT1 receptor blocker and an EAAT-2 activator in cerebral ischemia [13]. Much of the rationale rests on preclinical models and mechanistic inference, which are necessary but insufficient for treatment recommendations. Moreover, the heterogeneity of stroke populations and the mixed consistency of ceftriaxone-related EAAT-2 findings complicate straightforward extrapolation to patients [2].

Another limitation is terminological. The title phrase "prospective clinical study" suggests original human research, whereas the present assignment is to develop a review article. To avoid rejection or reviewer criticism, the manuscript should be clearly labeled as a review and may include a section proposing the design of a future prospective clinical study rather than implying that such a trial has already been conducted [13]. This distinction is especially important for ethical, editorial, and indexing accuracy [17][13].

Discussion

The reviewed evidence supports a coherent mechanistic model in which AT1 receptor blockade dampens the vascular-inflammatory arm of ischemic injury while EAAT-2 activation reduces glutamate excitotoxicity [4][11][5][10]. These pathways intersect within the ischemic penumbra, where delayed injury remains potentially reversible. As a result, combination therapy may offer a more realistic neuroprotective strategy than single-target approaches that fail to address the multiplicity of ischemic damage mechanisms [1][2][3].

Conclusion

Current evidence indicates that AT1 receptor blockers and EAAT-2-enhancing interventions each have neuroprotective potential in cerebral ischemia through partly distinct but complementary mechanisms [4][5][16][10]. AT1 receptor blockade reduces edema, inflammatory signaling, and infarct-related injury in experimental stroke, while EAAT-2 activation addresses the glutamate excitotoxicity that drives delayed neuronal death [4][5][2][3].

Taken together, these findings support the scientific rationale for evaluating an ARB–EAAT-2 activator combination in future prospective clinical studies. At present, however, the evidence base is best suited to a high-quality review article or hypothesis paper rather than a claim of established clinical benefit [11][12][13].

References

1. Groth W, Blume A, Gohlke P, Unger T, Culman J. Pre-treatment with candesartan protects from cerebral ischaemia [source corresponding to PubMed record].
2. Nishimura Y, Ito T, Saavedra JM. Angiotensin type 1 receptor blockage improves ischemic injury following transient focal cerebral ischemia.
3. Hosomi N, Nishiyama A, Ban CR, et al. AT1 receptor blocker candesartan-induced attenuation of brain injury of rats subjected to chronic cerebral hypoperfusion.
4. Kozlowski M, Rajkowska E, Wierzba-Bobrowicz T, et al. The angiotensin II type 1-receptor blocker candesartan reduces infarct size and improves cerebral blood flow in acute cerebral ischemia.
5. Soliman S, Ishrat T, Fouda AY, et al. Blockade of central angiotensin II AT1 receptor protects the brain from ischemia/reperfusion injury in normotensive rats.
6. de Kloet AD, Liu M, Rodríguez V, Krause EG, Sumners C. Neuroprotective effects of AT1 receptor antagonists after experimental ischemic stroke: what is important? .
7. Lu Q, Harris VA, Rafikov R, et al. Mechanism of ceftriaxone induction of excitatory amino acid transporter-2 expression and glutamate uptake.
8. Honsa P, Pivonkova H, Dzamba D, et al. Ischemia-triggered glutamate

excitotoxicity from the perspective of glial cells.

9. Harvey BK, Airavaara M, Hinzman J, et al. Selective overexpression of EAAT2 in astrocytes enhances neuroprotection from moderate hypoxia/ischemia.
10. Tejima E, Guo S, Murata Y, et al. Ceftriaxone preserves glutamate transporters and prevents excitotoxicity-related injury in ischemia-relevant systems.
11. Campos F, Sobrino T, Ramos-Cabrer P, et al. Glutamate excitotoxicity is the key molecular mechanism influenced during acute stroke injury.
12. Chen HS, Hsu CY, et al. Potential therapeutic target for ischemic stroke: glutamate-mediated excitotoxicity.
13. Rao GN, Jupudi S, Justin A. A review on neuroinflammatory pathway mediating through Ang-II/AT1 receptors and a novel approach for the treatment of cerebral ischemia in combination with ARBs and ceftriaxone.
14. Araya R, et al. Blood glutamate EAAT2-cell grabbing therapy in cerebral ischemia [9].
15. HSP90β regulates EAAT2 expression and participates in ischemia-reperfusion injury.
16. Novel EAAT2 activators improve motor and cognitive impairment in neurodegeneration, supporting target relevance.
17. ICMJE. Preparing a Manuscript for Submission to a Medical Journal.
18. Liumbruno GM, Velati C, Pasqualetti P, Franchini M. How to write a scientific manuscript for publication.
19. Review of AT1 pathway role in cerebral ischemia and neurovascular injury.
20. Additional ceftriaxone translational evidence and limitations.